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Giant Platelet Disorder in a Patient With Type 2B von Willebrand's Disease

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While patients with type 2B von Willebrand's disease often exhibit thrombocytopenia, platelet morphology is typically normal. We describe a 44-year-old Jamaican man with thrombocytopenia and a history of bleeding, who had giant platelets on his peripheral blood film. Functional studies and von Willebrand factor gene sequencing showed him to have type 2B von Willebrand's disease with a heterozygous point mutation resulting in a V553M (V1316M in the new von Willebrand factor gene mutation nomenclature) amino acid substitution. Family studies showed one of his two sisters to have an ill-defined giant-platelet-syndrome with mild thrombocytopenia, but not von Willebrand's disease, indicating that the association of giant platelets and von Willebrand's disease in our patient was most likely coincidental. This report describes the rare concurrence of two uncommon disorders. It also demonstrates how the thrombocytopenia of type 2B von Willebrand's disease can be misdiagnosed as ITP, leading to unnecessary and potentially harmful therapeutic interventions. Am. J. Hematol. 57:62–67, 1998. © 1998 Wiley-Liss, Inc.

Key words: von Willebrand's disease; thrombocytopenia; giant platelets

INTRODUCTION

Type 2B von Willebrand's disease is caused by an abnormal von Willebrand's factor molecule, which exhibits enhanced binding to platelets, leading to platelet clumping and thrombocytopenia. Platelet morphology is typically normal.

CASE REPORT

A 44-year-old Jamaican black man presented for evaluation of thrombocytopenia. At the age of 11 years he had a tooth extraction without significant bleeding. At the age of 14 years he developed hemarthrosis after a traumatic left knee injury. At the age of 21 years he was discharged from the military service because of incidentally discovered thrombocytopenia. No definitive diagnosis was made. Subsequently he had two tooth extractions, bleeding for 2 to 3 days after each procedure.

In January 1994 he presented with nontraumatic left knee hemarthrosis. His automated platelet count was 22,000/μL. A bone marrow aspirate and biopsy showed an adequate number of megakaryocytes of normal morphology. He was thought to have ITP and was started on prednisone, which he self-discontinued after a few days. He was lost to follow-up until he presented again in August 1994 with hematemesis, following the use of large amounts of aspirin-containing drugs for several months. His automated platelet count was 39,000/μL. Markedly enlarged platelets and some platelet clumping were noted on the peripheral blood film. He was admitted and treated with high-dose steroids for presumed ITP. Continued gastrointestinal bleeding from endoscopically diagnosed diffuse gastritis prompted platelet transfusions, but platelet count responses were always short-lived. He was thought to have steroid-unresponsive ITP and splenectomy was performed. No significant increase in his platelet count resulted. He was discharged on high-

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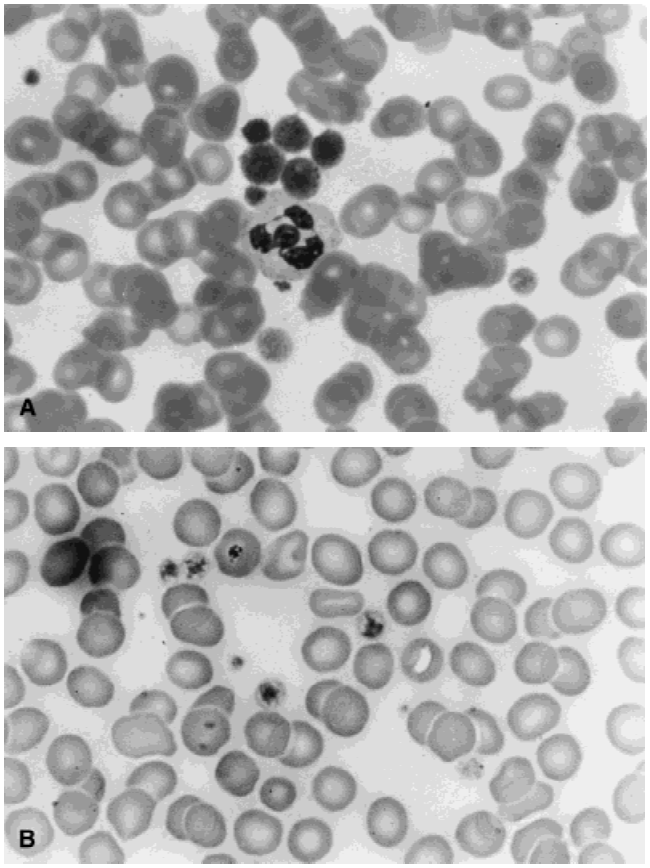

Fig. 1. Light-microscopical images of peripheral blood films after Giemsa stain. A cluster of very large platelets is seen in the patient's blood film (A). The platelets of Sister A (B) are also enlarged, but to a lesser degree.

dose oral prednisone and 4 weeks later his platelet count was 13,000/μl. He was referred for further evaluation of his thrombocytopenia.

There was no family history of bleeding. His father, who was deceased, was known to have had normal platelet counts. Platelet counts of his mother, who was also deceased, were not known. One sister was known to have normal platelet counts, his other sister's platelet count was unknown. Both sisters were subsequently tested (results described below). A paternal aunt was said to have been very light skinned and had blue eyes and light hair. All other family members were of normal Afro-Jamaican appearance. Physical examination of the patient was noncontributory. The hemoglobin was 10.9 g/dL, the white cell count 14.9 × 10^3/μL, and the automated platelet count 22,000/μL. Peripheral blood film showed red cell abnormalities consistent with his asplenic state. The platelet morphology was striking: most platelets were enlarged (Fig. 1A), most of them close to the size of red cells, some even larger than erythrocytes. All platelets were very granular and many of them showed coarse vacuolization. Several platelet aggregates of 5 to 6 platelets were present (Fig. 1), few aggregates of up to 25 platelets. The estimated platelet count was 40,000 to 50,000/μL. The mean platelet volum (MPV) of 6.9 fL, obtained with an automatic cell counter, did not indicate the true MPV, since most platelets were the size of red cells and were possibly counted and measured as such. The automated platelet distribution width (PDW) was very high. White blood cell morphology was normal and there were no abnormal cytoplasmic leukocyte inclusions on Giemsa stain or on electron microscopy. Review of the bone marrow aspirate and biopsy confirmed normal number and morphology of megakaryocytes. Prothrombin time and activated partial thromboplastin time were normal. The bleeding time was >15 min (normal <9.5 min). The interpretation of platelet aggregation studies (Fig. 2) was limited, since the patient had thrombocytopenia. However, there was an aggregation response to thrombin, ADP, collagen, arachidonic acid, epinephrine, and varying concentrations of ristocetin, including low-dose ristocetin at 0.5 mg/mL. There was no spontaneous aggregation after addition of cryoprecipitate.

Von Willebrand factor activity was 26% (nl 43–143%), von Willebrand factor antigen was 111% (nl 59–144%), and factor VIII activity level 79% (nl 61–158%). Von Willebrand factor multimer electrophoresis showed the absence of high molecular weight multimers (Fig. 3). To exclude pseudo-von Willebrand's disease, sequencing of the gene encoding for the glycoprotein Ibα chain was performed between nucleotide 637 (5′) and 1,110 (3′), which includes the region that is involved in binding of von Willebrand factor to the platelet [1]. This study was normal. PCR analysis of exon 28 of the von Willebrand gene [2] demonstrated abnormal cutting with the enzyme MvnI, consistent with a diagnosis of heterozygous type 2B von Willebrand's disease, most likely a V553M mutation. DNA gene sequencing of exon 28 [3] demonstrated a heterozygous state with a guanine (G) to adenine (A) nucleotide substitution at nucleotide 3,946, leading to a valine (V) to methionine M) aminoacid substitution, termed V553M in the old von Willebrand factor mutation nomenclature. In the new nomenclature [4], this mutation is termed G4196A and the aminoacid substitution is referred to as V1316M. Electron microscopy demonstrated enlarged platelets, many of them larger than erythrocytes (Fig. 4), without specific abnormalities. Dense bodies were present.

Laboratory testing was performed on the patient's two sisters (Table I). Sister A had a platelet count of 124,000/μL with a mean platelet volume (MPV) of 10.9 fL (normal 6.5–10.5 fL) with a high platelet distribution width (PDW). Sister B had a platelet count of 232,000/μL with a MPV of 8.2 fL and a normal PDW. Both had normal red and white cell counts. The peripheral blood film of sister A (Fig. 1B) showed that approximately 50% of all platelets were enlarged, many being half the diameter of erythrocytes; platelet enlargement was not as pronounced

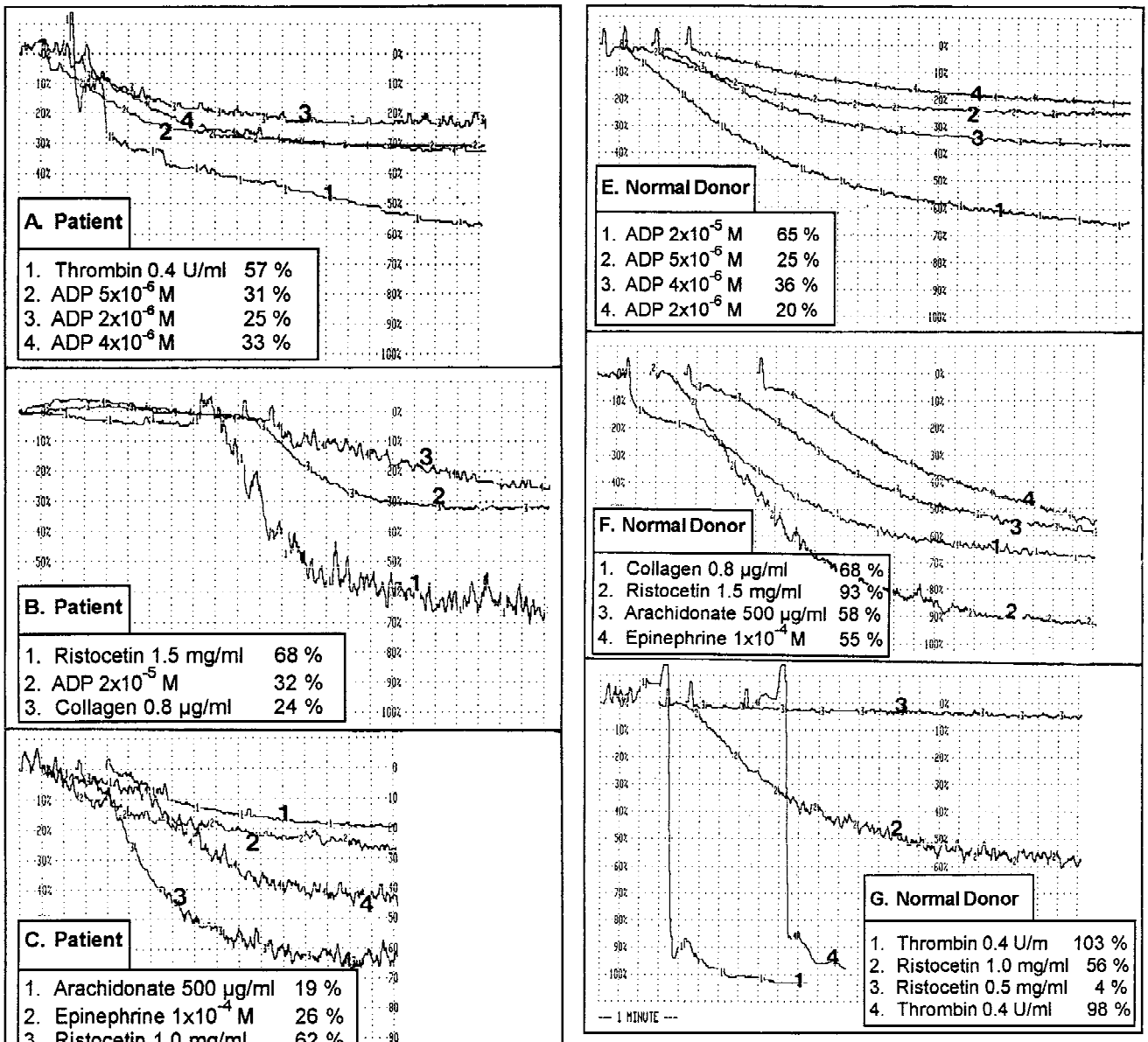

Fig. 2. Platelet aggregation study: Aggregation is seen with all agonists, including low-dose ristocetin; there is no spontaneous aggregation after addition of cryoprecipitate.

as in the patient and only an occasional platelet was the size of erythrocytes. The blood film of sister B showed normal-sized platelets. Neither blood film showed leukocyte or erythrocyte abnormalities. Von Willebrand studies were normal in both sisters. Platelet aggregation studies were not available.

DISCUSSION

Giant platelets are not a known feature of von Willebrand's disease and have only been reported once before in association with type 2B von Willebrand's disease. López-Fernández et al. [5] described two patients from a

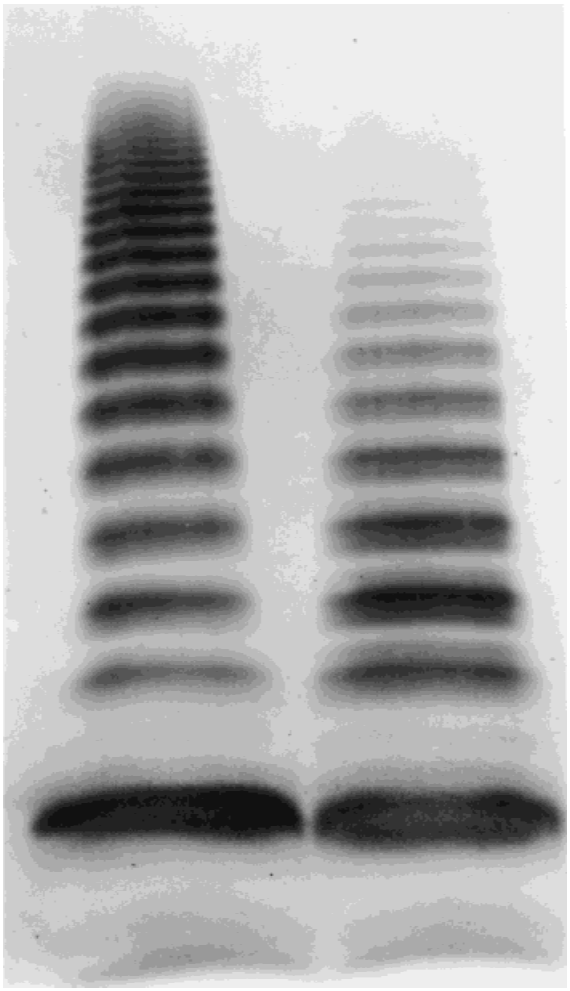

Fig. 3. Agarose multimer electrophoresis pattern of plasma vWf of a nomral control (left) and the patient (right). Large vWf multimers are absent in the patient.

single family who had type 2B von Willebrand's disease with thrombocytopenia, who had ''giant'' platelets on peripheral blood film with median platelet volumes between 21 and 23 fL. Electron microscopy of the platelets was unremarkable except for the platelets' size. Platelet aggregation studies showed a non-specific defect with reduced aggregation to multiple agonists. The authors speculated that the abnormal vWf may have caused not only thrombocytopenia, but also, by some unknown mechanism, morphological platelet changes. The significance of ''large'' platelets described by Saba et al. [6] in 5 family members with type 2B von Willebrand's disease and thrombocytopenia is unclear, since no actual platelet size was reported. Platelet aggregation studies with multiple agonists were ''normal to slightly decreased.'' The authors interpreted the large platelets as presumably being young circulating platelets secondary to an increased platelet turnover.

Our patient was found to have a V553M von Willebrand factor gene mutation (called V1316M in the new von Willebrand factor mutation nomenclature [4]). This specific mutation has been reported six times before in the literature: Lillicrap et al. [7] described eleven individuals from three families with this mutation, Randi et al. [2] one patient, Cooney et al. [3] four patients from three families, Piétu et al. [8] another patient, Murray et al. [9] five members of one family, and Eikenboom et al. another patient [10]. None of these patients were mentioned to have large platelets.

Platelet count and platelet volume tend to be inversely related in normal subjects as well as in subjects with a variety of hyperdestructive thrombocytopenias, such as ITP, vasculitis, prosthetic and severe rheumatic heart valve disease, diabetes mellitus with retinopathy, and disseminated intravascular coagulation [11,12]. However, platelet enlargement of the degree seen in our patient is not typically seen in these thrombocytopenias and suggests an additional defect. One of our patient's sisters also had large platelets on peripheral blood film, but did not have von Willebrand's disease. This suggests the presence of a familial giant platelet syndrome, independent of von Willebrand's disease. It can be speculated that the coincidental occurrence of type 2B von Willebrand's disease resulted in worsening of the thrombocytopenia and the increased platelet size of an underlying familial giant platelet syndrome.

A specific platelet defect or one of the better defined giant platelet syndromes could not be identified in our patient. Absence of leukocyte inclusions and of associated somatic defects ruled out May-Hegglin anomaly, Epstein's syndrome, Fechtner syndrome, and Sebastian platelet syndrome [13]. Presence of an aggregation response to ristocetin excluded Bernard-Soulier syndrome (congenital absence of glycoprotein Ib) [14] and the appearance of the platelets on the peripheral blood film and the presence of α-granules on electron microscopy excluded the gray platelet syndrome [14]. The Montreal platelet syndrom is characterized by the presence of giant platelets and spontaneous platelet aggregation on aggregometer testing [15], which our patient did not have. The description of a very light-skinned family member with blue eyes and light hair in our patient's Afro-Jamaican family brings Hermansky-Pudlak syndrome to mind; however, in this syndrome of albinism and thrombocytopathy with platelet aggregation abnormalities, giant platelets have not been described. Furthermore, our patient did not show the typical platelet storage pool defect with deficiency of dense granules that leads to normal primary aggregation with ADP and epinephrine, but no second phase of aggregation [16]. Najean and Lecompte described a group of patients with congenital thrombocytopenia, who had enlarged platelets (range 10–18 fL) and normal platelet function and platelet survival, and demonstrated autosomal dominant transmission in all of the cases in which a family survey could be per-

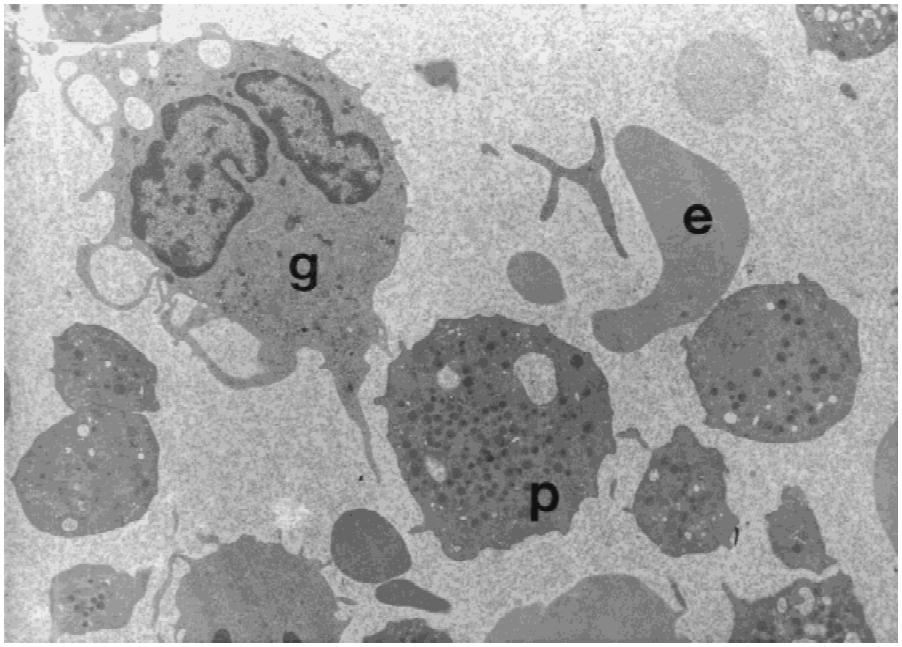

Fig. 4. Electron-microscopical image of the patient's peripheral blood. The platelets are markedly enlarged; several exceed the size of erythrocytes. Nonspecific vacuolization is seen. p = platelet; e = erythrocyte; g = granulocyte.

TABLE I. Summary of Laboratory Results of the Patient and His Two Sisters*

	Platelet count (/μL)	Peripheral blood film	vWf antigen (nl: 59–144%)	vWf activity (nl: 43–143%)	vWF multimers
Patient	≈50,000	Giant platelets, platelet clumps	111%	26%	Absence of HMWM
Sister A	124,000	Large platelets	157%	191%	Normal
Sister B	232,000	Normal platelets	224%	335%	Normal

*vWf, von Willebrand factor; nl, normal; HMWM, high molecular weight multimers.

formed [17]. It is not known whether this represents a uniform platelet disorder.

The case presented describes the rare association of type 2B von Willebrand's disease with a giant platelet syndrome. The presence of giant platelets in our patient appears to be coincidental and not a feature of the specific von Willebrand factor mutation that he had. The case also demonstrates the importance of family studies and illustrates how the thrombocytopenia of type 2B von Willebrand's disease can be misdiagnosed as ITP and refractory ITP, leading to unnecessary and potentially harmful therapeutic interventions.

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